Revision of EPA 1-liners pertaining to the EPA Memorandum (1/24/89) was performed (12/19/89) by M. Silva.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

DIPHENAMID

SB 950-048, Tolerance # 230
Chemical Code #: 000226

July 29, 1986
Revised December 10, 1987
Revised December 19, 1989

I. DATA GAP STATUS

Chronic rat: Data gap, inadequate study, no adverse effect indicated.

Chronic dog: Data gap, inadequate studies, no adverse effect indicated.

Onco rat: Data gap, inadequate study, no adverse effect indicated.

Onco mouse: Data gap, no study on file.

Repro rat: Data gap, inadequate studies, no adverse effect indicated.

Terato rat: Data gap, inadequate studies, no adverse effect indicated.

Terato rabbit: Data gap, inadequate study, no adverse effect indicated.

Gene mutation: Data gap, inadequate studies, no adverse effect indicated.

Chromosome: Data gap, no study on file.

DNA damage: Data gap, inadequate study, no adverse effect indicated.

Neurotox: Not required at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name: T891219
Revised 12/89 by M. Silva
Rectified through volume #: 030 and record #: 936356 & 058603.

I. TOXICOLOGY SUMMARY

CHRONIC, RAT

005 006432 "Chronic Toxicity in Rat With U-4513," (Upjohn Company, Kalamazoo, MI, 1/64). Rats were given 1, 3, 10 or 30 mg/kg/day by oral route (10/sex/group). **Unacceptable**, not a chronic study (90 days). Negative for adverse effect but insufficient information to evaluate. JW, 3/15/85.

021 010773 "Subchronic Oral Toxicity of Diphenamid Technical in Rats and Dogs," (Upjohn Company, Kalamazoo, MI, 5/83). **Unacceptable**, brief summary. Negative for reported adverse effect but insufficient information to evaluate. JW, 3/14/85.

025 036073 "Diphenamid - Safety Evaluation by Dietary Feeding to Rats for 101 Weeks - Final Report," (Woodard Research Corporation Laboratory and Consulting Service, Herndon, VA, 10/66). Accompanies summary 009 936327 (JW, 3/15/85). Charles River rats 30/sex/group were fed 3, 10 or 30 mg/kg/day for two years. **Unacceptable**, inadequate number of animals, doses not justified and no toxicity reported, no summary of neoplastic findings, no analysis of diet. No adverse effect reported. Evidence of pulmonary infection. JR, 3/14/86.
EPA 1-liner: Core Supplementary (as a rat oncogenicity study only).

009 046068 (936327) "Dietary Feeding to Rats for 101 Weeks (3/16/67, 7F0585)," is a summary of 025 036073. M. Silva, 12/19/89.

CHRONIC DOG

005 006428 "Chronic Oral Toxicity in Dog (74 Day Study With U-4513)," (Upjohn Company, Kalamazoo, MI, 4/63). Subchronic study (74 days). **Unacceptable**, insufficient information to evaluate but no adverse effect reported. JW, 3/15/85.

005 006431 "Chronic Oral Toxicity in the Dog With U-4513 (94 days)," Upjohn Company, Kalamazoo, Mi, 2/64. Subchronic study (94 days). **Unacceptable**, insufficient information to evaluate but no adverse effect reported. JW, 3/15/85.

021 010773 "Subchronic Oral Toxicity of Diphenamid Technical in Rats and Dogs," (Upjohn Company, Kalamazoo, MI, 5/83). Summary. **Unacceptable**, with insufficient information and no adverse effect reported. JW, 3/14/85.

025 036074 "Diphenamid - Safety Evaluation by Dietary Feeding to Dogs For 103 Weeks. Final Report (Oncogenicity), (Enide Technical)," (Woodard Research Corporation Laboratory and Consulting Service, Herndon, VA, 10/66). Accompanies document 009 936327 (JW, 3/15/85). Beagles (3/sex/group) were fed 3, 10 or 30 mg/kg/day for 2 years. **Unacceptable**, no dose justification and no evidence m.t.d. was achieved, no diet analysis or purity of a.i., minimal histopathology. No adverse effect or clinical finding is reported. JR, 3/14/86.
EPA 1-liner: Core Minimum; NOEL = 120 ppm (3 mg/kg/day)--slightly increased liver/body weight and slight chronic inflammatory cell infiltrates in the livers, described as slight increase of portal macrophages and/or infiltrates were seen in the 400 and 1200 ppm groups.

009 046069 (936327) "Dietary Feeding to Dogs for 103 Weeks (3/16/67, 7F0585)," is a summary of 025 036074. M. Silva, 12/19/89.

ONCOGENICITY, RAT

No study on file.

009 046068 (936327) "Dietary Feeding to Rats for 101 Weeks (3/16/67, 7F0585)," is a summary of 025 036073. M. Silva, 12/19/89.

EPA 1-liner: "Diphenamid - Safety Evaluation by Dietary Feeding to Rats for 101 Weeks - Final Report," (Woodard Research Corporation Laboratory and Consulting Service, Herndon, VA, 10/66) 025 036073 was considered to be Core Supplementary (as a rat oncogenicity study only) by EPA.

ONCOGENICITY, MOUSE

No study on file.

REPRODUCTION, RAT

021 010775 1966, Upjohn; JW, 3/14/85. Summary. **Unacceptable**, No adverse effect reported.

007 936318 No date, Lilly; JW, 3/15/85. **Unacceptable**, inadequate number of animals, two doses only, no individual data. Positive adverse effects were reported for lower viability and lactation index at 2500 ppm (0.25%) in both Fo and F1. Six males and 12 females per group were fed 0, 0.05 or 0.25% in the diet for 2 generations, 2 litters. NOEL = 500 ppm. Decreased body weight gain in both sexes at 2500 ppm indicates an adequate dose was approached. Reevaluation of the study by JR and JP, 3/31/86, finds that while the viability index (62% versus 87%) and the lactation index are lower, there is insufficient data to evaluate the significance and the role of maternal toxicity. In addition, survival in the

controls was lower than expected suggesting a husbandry problem. A second study, 036075 (see below) at slightly lower doses, reported no reproductive effects. Hence, a conclusion of no significant adverse effect is found. A Supplemental Review Worksheet is on file.

025 036075 "Diphenamid - Three-Generation Reproduction Study in Rats. (Enide Technical)," (Woodard Research Corporation Laboratory and Consulting Service, Herndon, VA, 10/66). Accompanies document 009 936327 (JW, 3/15/85). Charles River rats (10 males and 20 females/group) were fed 0, 10 and 30 mg/kg for 3 generations, 2 litters each. **Unacceptable** (no justification of dose, two doses only with no evidence m.t.d. was approached, diets were not analyzed and no histopathology was performed on P0). No adverse reproductive effect (including viability and lactation indices) was reported.
EPA 1-liner: Core Minimum; reproductive NOEL = 30 mg/kg (HTD), systemic NOEL = 10 mg/kg (slight liver congestion, slight to moderate hepatic cell glycogen depletion and irregularity of hepatic cell size was noted only in the weanlings of the F3 generation).

009 046070 (936327) "Three-Generation Reproduction Study in Rats (3/16/67, 7F0585)," is a summary of 025 036075. M. Silva, 12/19/89.

TERATOLOGY, RAT

005 006430 "Pregnancy Inhibition and Vaginal Cytology Assays in Rats With U-4513," (Upjohn Company, Kalamazoo, MI, 7/63). **Unacceptable** with insufficient information and no adverse effect reported. Three rats were dosed at 10 mg/kg/day by subcutaneous route for 7 days starting at day of mating. JW, 3/15/85.

030 058601, 058602 "Technical Diphenamid: Teratology Study in the Rat," (Life Science Research LTD., 5/6/86). Diphenamid technical (Code/batch No. CR 20655/2; Purity = 99.8%) was

administered daily, by gavage at 0 (1% w/v methylcellulose in distilled water), 25, 75 and 225 mg/kg/day to 21 mated rats/dose from days 6 to 15 of gestation. **No adverse effects indicated.** Maternal NOEL = 75 mg/kg/day (decreased body weight gain). Developmental NOEL = 75 mg/kg/day (lower fetal weight, decreased degree of ossification, increased incidence of space between body wall and organs, hydroureter, and hemorrhage). **Unacceptable**. Individual fetuses, their weights and number of effects/specific individual fetus not submitted. **Upgradable.** M. Silva, 12/10/87.

SUMMARY: Both studies were found unacceptable, due to insufficient information reported and therefore, even collectively are not sufficient to fill the data gap. There is the possibility of #058601 being upgraded if the additional information requested is provided. No adverse effects were indicated in either study.

TERATOLOGY, RABBIT

030 058603, 058604 "Technical diphenamid: Effect on pregnancy of the rabbit (Teratology study) -- Final report," (Huntingdon Research Centre, 3/19/87). Diphenamid technical: code/batch nos. CR 20655/1 (99.9% pure) and CR 20655/2 (99.5% pure) was administered by gavage at doses of 0 (0.5% carboxymethyl cellulose), 150, 300 and 600 mg/kg/day to 26, 23, 24 and 24 (respectively) mated rabbits from day 6 through day 18 of gestation. Day of confirmed mating = day 0 of gestation. **No adverse effect.** Maternal NOEL = 150 mg/kg/day (decrease in body weight gain and food consumption). Developmental NOEL $\geq$ 600 mg/kg/day. **Not acceptable.** Individual fetuses, their weights and number of effects/specific individual fetus not submitted. **Upgradable.** M. Silva, 12/10/87.

MUTAGENICITY, GNMU

Bacteria

021 010774 "Mutagenicity Tests of Diphenamid Technical Using Bacillus Subtilis, Salmonella Typhimurium and Escherichia Coli (Ames Test)," Upjohn Company, Kalamazoo, MI, 5/83. Summary. **Unacceptable** with insufficient information but no mutagenic effect reported for S. typhimurium, E. coli or B. subtilis. JW, 3/14/85.

025 036076 "Mutagenic Study on Diphenamid Using Microbes - Final Report (Reversion Plate Assay With Bacillus Subtilis, Escherichia Coli and Salmonella Typhimurium)," Institute of Environmental Toxicology, Tokyo, Japan. Salmonella. **Unacceptable**, no repeat trial, duplicate plates only. No increase in reversion rate is reported. Salmonella, 5 strains, were exposed to 0, 10, 50, 500, 1000 and 5000 ug/plate with and without activation. JR, 3/14/86.

MUTAGENICITY, CHROMOSOMES

No study on file.

MUTAGENICITY, DNA

Bacillus subtilis

025 036077 "Mutagenic Study on Diphenamid Using Microbes - Final Report (Rec-Assay With Bacillus Subtilis, Escherichia Coli and Salmonella Typhimurium," (Institute of Environmental Toxicology, Tokyo, Japan, 7/78). **Unacceptable** (no activation included, no replicates). No

differential growth effect is reported. B. subtilis H17 and M45 were exposed by disk assay to 20, 100, 200, 500, 1000 and 5000 ug/disk. JR, 3/14/86.